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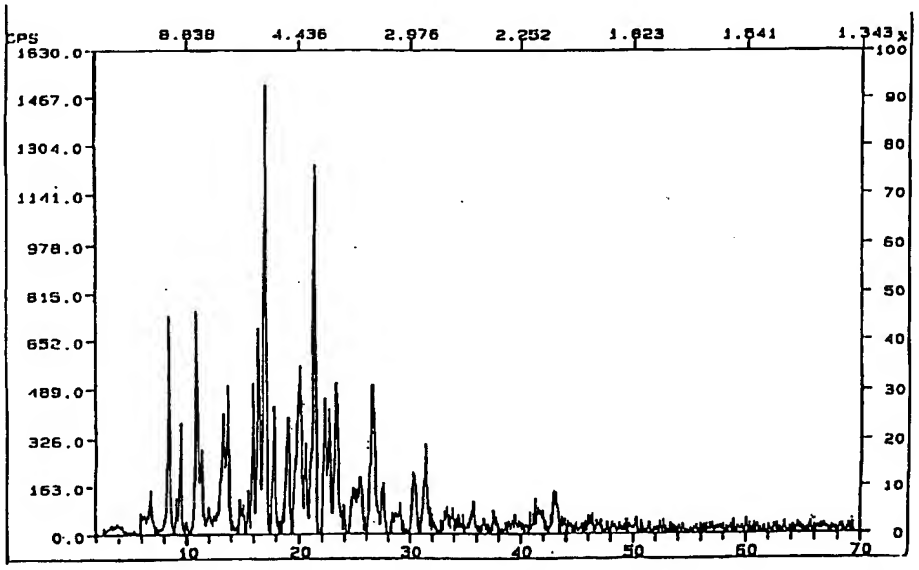
(54) Title: CRYSTAL MODIFICATION



(57) Abstract: A novel crystal form of, α-dimethyl-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl]benzeneacetic acid hydrochloride, processes for its preparation and its pharmaceutical use are disclosed.

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Crystal Modification

Summary

This invention relates to a novel crystal form of α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride, a process for its preparation and pharmaceutical formulations thereof.

Background

The compound α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride has been named according to the U.S.A.N. as fexofenadine hydrochloride ("F-HCl"). It is known as the active metabolite of the non-sedating antihistamine terfinadine and is itself marketed in the United States as a non-sedating antihistamine. F-HCl and its preparation are described, for example, in U.S Patent No. 5,578,610, which is here incorporated by reference. Anhydrous and hydrated crystal forms of F-HCl identified as Forms I, II, III and IV are described in WO 95/31437.

The present invention relates to a novel F-HCl crystal modification, hereinafter designated as Form A, which is distinguished from previously known crystal forms by physical and spectroscopic properties such as melting point, x-ray powder diffraction pattern, solid state NMR spectrum and infrared spectrum. The Form A crystal modification of F-HCl is prepared in an advantageously environmentally friendly manner.

Brief Description of the Drawings

Figure 1 shows the powder x-ray diffraction pattern of the Form A crystal modification of F-HCl (λ=1.540600).

Figure 2 shows the solid state Carbon-13 NMR of the Form A crystal modification of F-HCl over the chemical shift range of 275 to –100 ppm.

Figure 3 shows the FTIR spectrum of the Form A crystal modification of F-HCl as a mull with Nujol oil.

Figure 4 shows the FTIR spectrum of Nujol oil.

Detailed Description

The Form A crystal modification of F-HCl is characterized by its physical and spectroscopic properties which are described in detail below.

The Form A crystal modification of F-HCl has a characteristic melting point in the range from about 138°C to 148°C, more specifically about 142°C to about 145°C.

Figure 1 is the powder x-ray diffraction pattern of the Form A crystal modification of F-HCl. The powder x-ray diffraction pattern of Form A is characterized by peaks at about 10.5, 8.1, 5.5, 5.4, 5.2, 4.42, 4.15, 3.82, 3.35 d-spacing units. The x-ray diffraction pattern depicted in Figure 1 is summarized in Table 1:

Table 1 – Powder X-Ray Diffraction Peaks for the Form A crystal modification of F-HCl

Peak No.	°2θ[1]	d-space[1]	RELATIVE[2] INTENSITY	Peak No.	°2θ[1]	d-space[1]	RELATIVE[2] INTENSITY
1	5.99	14.74	4	23	21.38	4.15	82
2	6.59	13.40	4	24	22.27	3.98	28
3	6.83	12.91	9	25	22.68	3.91	27
4	8.42	10.49	45	26	23.29	3.81	33
5	9.09	9.71	7	27	24.82	3.53	9
6	9.47	9.32	23	28	25.03	3.55	9
7	10.85	8.14	48	29	25.45	3.49	12
8	11.29	7.83	18	30	26.55	3.35	33
9	11.97	7.39	5	31	27.50	3.24	11
10	12.45	7.09	4	32	29.09	3.06	6
11	13.26	6.66	26	33	30.31	2.94	13
12	13.67	6.46	31	34	31.40	2.34	17
13	14.80	5.93	7	35	31.82	2.81	5
14	15.08	5.86	6	36	33.34	2.68	5
15	15.54	5.69	9	37	35.66	2.51	5
16	15.97	5.54	31	38	35.78	2.50	5
17	16.46	5.37	44	39	41.29	2.13	6
18	17.02	5.29	100	40	41.55	2.17	5
19	17.80	4.97	27	41	41.73	2.16	5
20	19.01	4.65	26	42	42.90	2.13	9
21	20.05	4.42	36	43	43.09	2.09	9
22	20.57	4.31	19				

1 – peak values reported in Table 1 are truncated to 2 decimal places from the instrument report and reported without regard to significant figures

2 – Intensities may vary significantly due to orientation effects

Variances in the d-spacing values reported for any x-ray diffraction p ak within ± 1% are considered insignificant. The use of the expression "about" when describing the position of an powder x-ray diffraction peak is intended to provide a basis for including such insignificant variances within the characterization of the Form A crystal modification.

Figure 2 shows the carbon-13 NMR spectrum of the Form A crystal modification of F-HCl measured using 600 transients and a 6 second pulse delay over the chemical shift range of 275 to –100 ppm. Characteristic signals are observed at chemical shifts of 187.4, 180.3, 74.5, 48.8, and 29.8 ppm. Table 2 summarizes the signals observed in the solid state carbon-13 NMR of the Form A crystal modification of F-HCl.

Table 2 – Solid State NMR Signals of The Form A crystal modification of F-HCl

peak #	p.p.m.	peak #	p.p.m.
1	187.4	12	53.9
2	180.3	13	48.8*
3	148.3	14	43.2
4	145.6	15	40.2
5	142.0	16	36.5
6	130.4*	17	32.9
7	128.2*	18	29.8
8	126.4*	19	26.0*
9	78.9*	20	24.6*
10	74.5	21	22.6
11	57.5		

* denotes most intense signals

The chemical shifts reported for solid state carbon-13 NMR signals can vary from sample to sample by up to 1 ppm. The use of the expression "about" to describe the chemical shift of an NMR signal is intended to include such variances within the characterization of the Form A crystal modification.

One or more of the physical properties and/or spectroscopic properties are the basis for characterizing the Form A crystal modification of F-HCl.

For example, the Form A crystal modification of F-HCl is properly described as α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride having a melting point in the range from 138°C to 148°C, or as α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride having a melting point in the range from about 142°C to about 145°C. It is also properly described as crystalline α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride having powder x-ray diffraction peaks at d spacings of 10.5, 8.1, 5.5, 5.4, 5.2, 4.42, 4.15, 3.82, 3.35 or the x-ray diffraction pattern depicted in Table 1. It is also properly described as α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride having solid state carbon-13 NMR signals at chemical shifts of 187.4, 180.3, 74.5, 48.8, and 29.8 ppm, or as having the solid state carbon-13 NMR spectrum depicted in Figure 2 and Table 2. It is also properly described as α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride having the Fourier Transform Infrared Spectrum depicted in Figure 3A as a Nujol oil mull.

The Form A crystal modification is also properly described by a combination of physical and/or spectroscopic properties.

Thus, Form A F-HCl is a substantially pure crystal modification of α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride characterized by powder x-ray diffraction peaks at d spacings of about 10.5, 8.1, 5.5, 5.4, 5.2, 4.42, 4.15, 3.82, 3.35 and a melting point in the range from about 142°C to about 145°C.

Form A F-HCl is also a crystal modification of α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride characterized by solid state carbon-13 NMR signals at chemical shifts of about 187.4, 180.3, 74.5, 48.8, and 29.8 ppm and powder x-ray diffraction peaks at d spacings of

about 10.5, 8.1, 5.5, 5.4, 5.2, 4.42, 4.15, 3.82, 3.35. It is also such a crystal modification having a melting point in the range from about 142°C to about 145°C in pure form.

Form A F-HCl is also properly described as a crystal modification having the solid state carbon-13 NMR spectrum depicted in Figure 2 and the x-ray powder diffraction pattern depicted in Figure 1. It is also such a crystal modification having the Fourier Transform Infrared Spectrum depicted in Figure 3A as a Nujol oil mull and can be further characterized as having a melting point in the range from 138°C to 148°C in substantially pure form, preferably from about 142°C to about 145°C in pure form.

Preferably, the Form A crystal modification of F-HCl is in substantially pure form - substantially pure form being intended to mean that at least 80 percent by weight of the crystalline F-HCl in the sample is present as Form A. Most preferably, the Form A crystal modification is in pure form meaning that at least 90% of the crystalline F-HCl in the sample is present as Form A. The present invention also relates to highly pure Form A crystal modification meaning that the material is essentially homogeneous Form A crystal modification.

The Form A crystal modification of F-HCl is prepared in an environmentally friendly manner by crystallization from an aqueous solution of F-HCl at a temperature in the range from 5°C to 50°C, preferably in the range from 20°C to 40°C. Generally, a temperature of about 30°C is optimal. If the crystallization is carried out at the higher and lower temperatures in the above defined temperature ranges the resulting product can be a mixture of crystal forms which includes Form A.

Generally, crystalline or non-crystalline F-HCl is dissolved in water with stirring to form an aqueous solution of F-HCl. The temperature of the aqueous solution of F-HCl is then adjusted to the desired temperature range, for example, by placing it in a water or oil bath, the solution is stirred and the water allowed to partially evaporate to yield Form A crystals of F-HCl. Preferably, the evaporation of the water is assisted, for example, by passing a gentle stream of air over the surface of the solution or reducing the pressure above the solution. However, the solution should be maintained in the temperature ranges identified above while the water evaporates from the solution.

Advantageously, no co-solvent or additional organic material is present in the water used to prepare the aqueous solution. However, minor amounts of such co-solvents or additional organic materials are not known to cause any significant disadvantage.

Thus, the present invention relates to a method of preparing the Form A crystal modification of α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride, which comprises preparing an aqueous solution of α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride; and crystallizing the α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride from the aqueous solution at a temperature of from 5°C to 50°C. Preferably, the crystallization is carried out at a temperature of 20°C to 40°C. Optimally, the crystallization is carried out at a temperature in the range from 25°C to 35°C, most optimally at about 30°C.

The crystallization step is effected by methods known in the art for precipitating a solute from solution, for example, by reducing the volume of solvent by evaporation or other means, or by addition of a co-solvent which induces crystallization and seeding.

Preferably, the crystallization step is effected by reducing the volume of water in the aqueous solution. Thus, the present invention further relates to a process wherein the crystallization step is effected by reducing the volume of water in the aqueous solution by an amount sufficient to promote crystallization. Preferably, the volume of water is reduced by evaporation of the water. This can be assisted by blowing a stream of air over the surface of the aqueous solution or by reducing the pressure above the solution in some other way.

The Form A crystal modification of F-HCl is used, in particular, for the preparation of pharmaceutical compositions of F-HCl. Thus, the present invention further relates to a pharmaceutical composition which comprises a pharmaceutically effective amount of the Form A crystal modification of α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride. Preferably, the pharmaceutically effective amount is the amount required to deliver 50 to 150 mg/day.

The following exampl is intended to illustrate, but not limit, the invention. All melting points are uncorrected unless otherwise noted.

Example 1

A 0.51 gram sample of F-HCl (melting point range from 192°C to 198°C) is dissolved in 100 mL of deionized water by heating on a water bath at 80°C and stirring at moderate speed with a 1 cm Teflon coated magnetic stirring bar. The temperature of the aqueous solution is reduced to 30°C and held at that temperature in the water bath as a gentle stream of air is passed over the surface. After about half of the water evaporates (approximately 7 hours), the crystalline precipitate of Form A F-HCl is separated by vacuum filtration with a Hirsch funnel. The sample is protected from dust by a filter paper cover and allowed to dry in the air for approximately 48 hours.

The Form A F-HCl thus prepared exhibits a melting point of 142°C to 145°C, determined in an open glass capillary suspended in circulating oil using a Thomas Hoover Melting Point Apparatus, the powder x-ray diffraction pattern is depicted in Figure 1 and Table 1, the solid state carbon-13 NMR spectrum depicted in Figure 2 and Table 2, and the FTIR spectrum depicted in Figure 3 as a Nujol mull.

Advantageously, no co-solvent or additional organic material is present in the water used to prepare the aqueous solution. However, minor amounts of such co-solvents or additional organic materials are not known to cause any significant disadvantage.

Thus, the present invention relates to a method of preparing the Form A crystal modification of α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride, which comprises preparing an aqueous solution of α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride; and crystallizing the α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride from the aqueous solution at a temperature of from 5°C to 50°C. Preferably, the crystallization is carried out at a temperature of 20°C to 40°C. Optimally, the crystallization is carried out at a temperature in the range from 25°C to 35°C, most optimally at about 30°C.

The crystallization step is effected by methods known in the art for precipitating a solute from solution, for example, by reducing the volume of solvent by evaporation or other means, or by addition of a co-solvent which induces crystallization and seeding.

Preferably, the crystallization step is effected by reducing the volume of water in the aqueous solution. Thus, the present invention further relates to a process wherein the crystallization step is effected by reducing the volume of water in the aqueous solution by an amount sufficient to promote crystallization. Preferably, the volume of water is reduced by evaporation of the water. This can be assisted by blowing a stream of air over the surface of the aqueous solution or by reducing the pressure above the solution in some other way.

The Form A crystal modification of F-HCl is used, in particular, for the preparation of pharmaceutical compositions of F-HCl. Thus, the present invention further relates to a pharmaceutical composition which comprises a pharmaceutically effective amount of the Form A crystal modification of α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride. Preferably, the pharmaceutically effective amount is the amount required to deliver 50 to 150 mg/day.

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The Form A F-HCl thus prepared exhibits a melting point of 142°C to 145°C, determined in an open glass capillary suspended in circulating oil using a Thomas Hoover Melting Point Apparatus, the powder x-ray diffraction pattern is depicted in Figure 1 and Table 1, the solid state carbon-13 NMR spectrum depicted in Figure 2 and Table 2, and the FTIR spectrum depicted in Figure 3 as a Nujol mull.

We claim:

1. The compound α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride having a melting point in the range from 138°C to 148°C.

2. The compound α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride having a melting point in the range from about 142°C to about 145°C.

3. A crystal modification of α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride characterized by powder x-ray diffraction peaks at d spacings of about 10.5, 8.1, 5.5, 5.4, 5.2, 4.42, 4.15, 3.82, 3.35.

4. The crystal modification of claim 3 having the powder x-ray diffraction pattern depicted in Figure 1.

5. The crystal modification of claim 3 characterized by a melting point in the range from about 142°C to about 145°C.

6. A crystal modification of α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride characterized by solid state carbon-13 NMR signals at chemical shifts of about 187.4, 180.3, 74.5, 48.8, and 29.8 ppm.

7. The crystal modification of claim 6 having the solid state carbon-13 NMR spectrum depicted in Figure 2.

8. The crystal modification of claim 6 having powder x-ray diffraction peaks at d spacings of about 10.5, 8.1, 5.5, 5.4, 5.2, 4.42, 4.15, 3.82, 3.35.

9. The crystal modification of claim 8 having a melting point in the range from about 142°C to about 145°C.

10. The crystal modification of claim 8 having a melting point in the range from about 138°C to 148°C.

11. The crystal modification of claim 7 having the powder x-ray diffraction pattern depicted in Figure 1.

12. The crystal modification of claim 11 having the Fourier Transform Infrared Spectrum depicted in Figure 3 as a Nujol oil mull.

13. The crystal modification of claim 12 having a melting point in the range from about 138°C to about 148°C in substantially pure form.

14. The crystal modification of claim 13 having a melting point in the range from about 142°C to about 145°C in pure form.

15. The crystal modification of claim 14 in highly pure form.

16. A process for preparing the Form A crystal modification of α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride, which comprises

(a) preparing an aqueous solution of α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride; and

(b) crystallizing the α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride from the aqueous solution at a temperature of from 5°C to 50°C.

17. A process of claim 16 wherein the temperature is in the range from 20°C to 40°C.

18. A process of claim 17 wherein the temperature is in the range from 25°C to 35°C.

19. A process of claim 18 wherein the temperature is about 30°C.

20. A process of claim 16 wherein the crystallization step is effected by reducing the volume of water in the aqueous solution by an amount sufficient to promote crystallization.

21. A process of claim 19 wherein the crystallization step is effected by reducing the volume of water in the aqueous solution by an amount sufficient to promote crystallization.

22. A process of claim 21 wherein the volume of water is reduced by evaporation.

23. A process of claim 16 wherein the α,α-dimethyl-4-{1-hydroxy-4-{4-(hydroxydiphenylmethyl)-1-piperidinyl}butyl}benzeneacetic acid hydrochloride produced is pure Form A crystal modification.

FIGURE 1

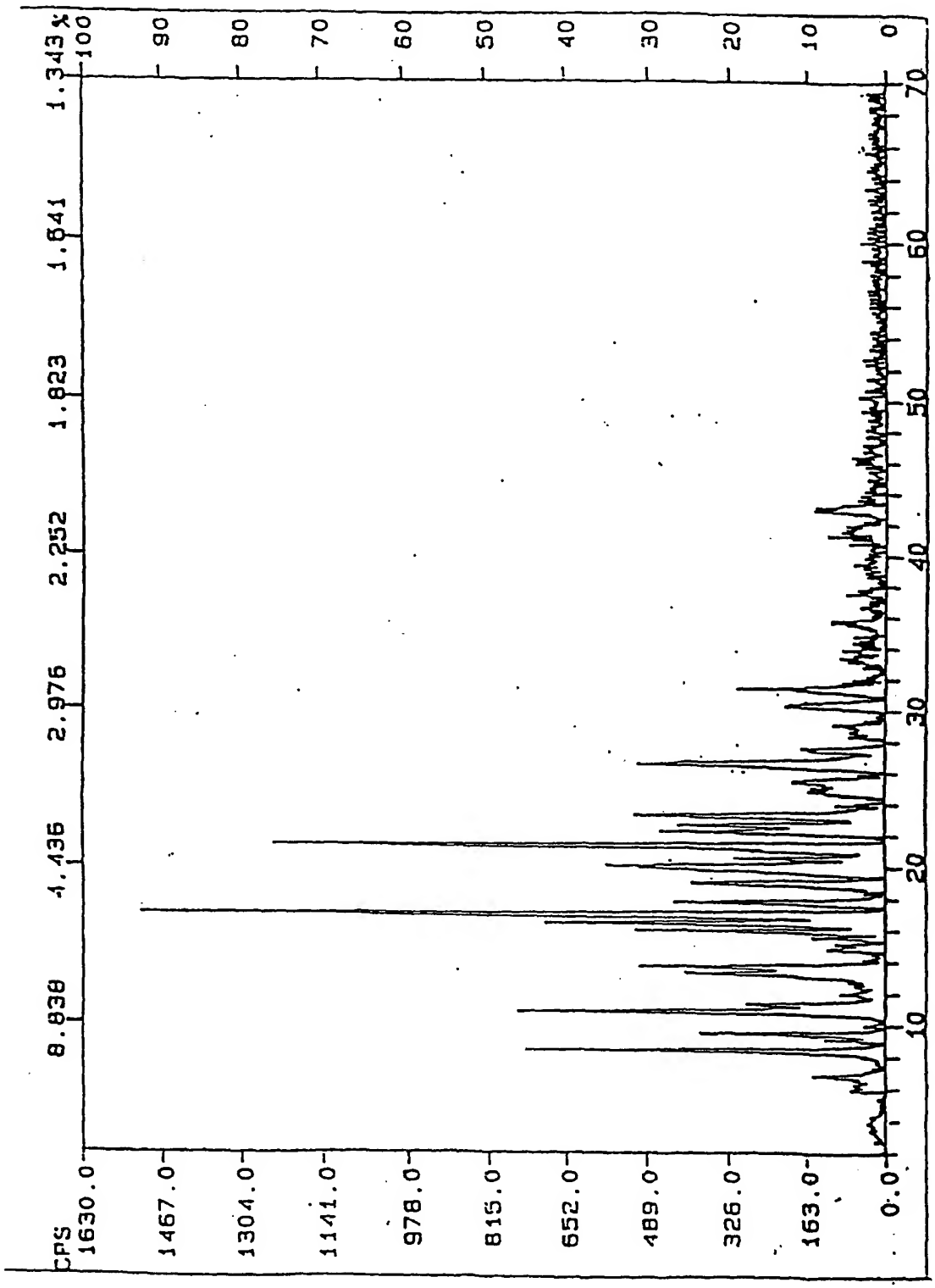
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FIGURE 2

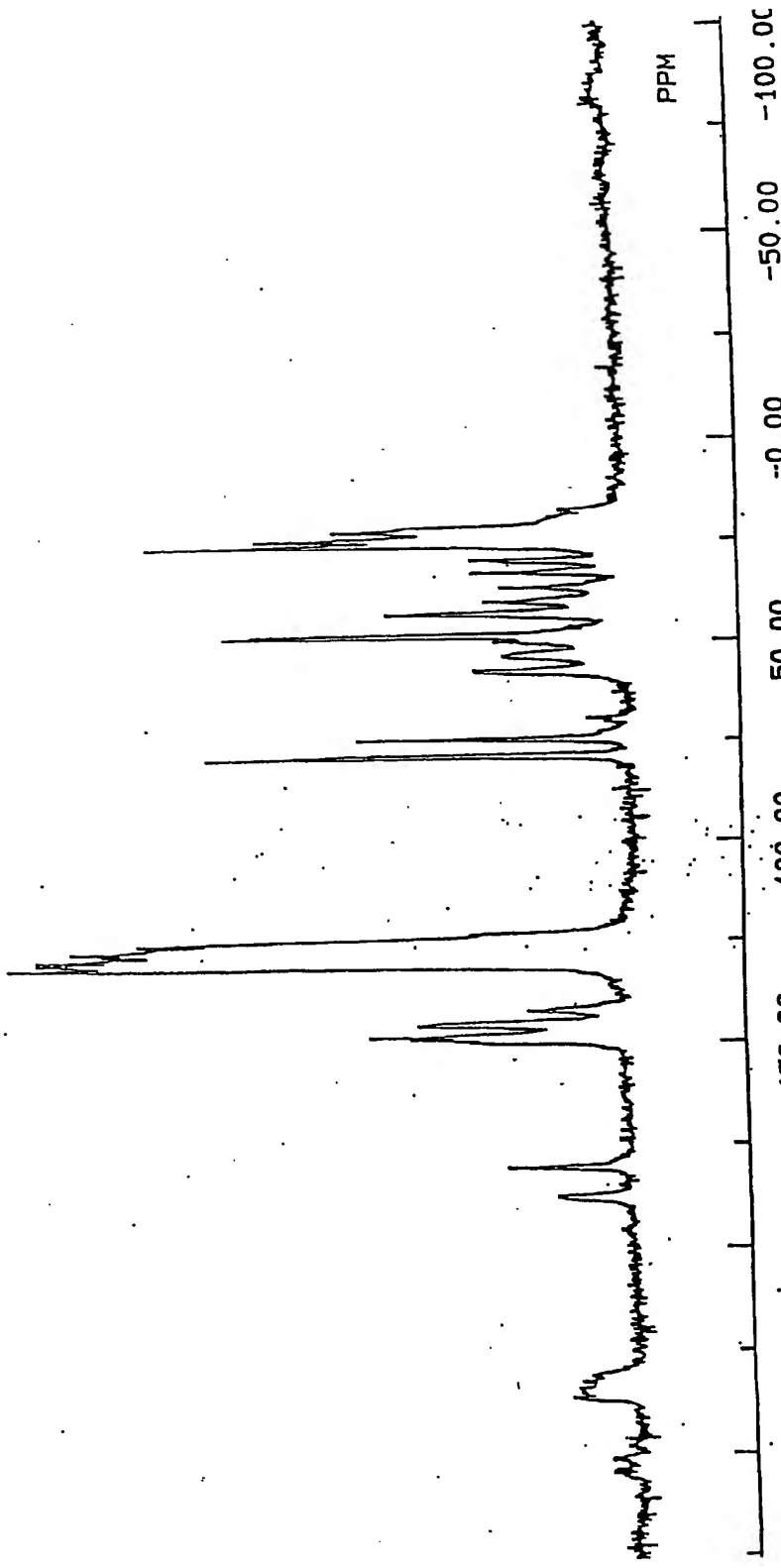


FIGURE 3

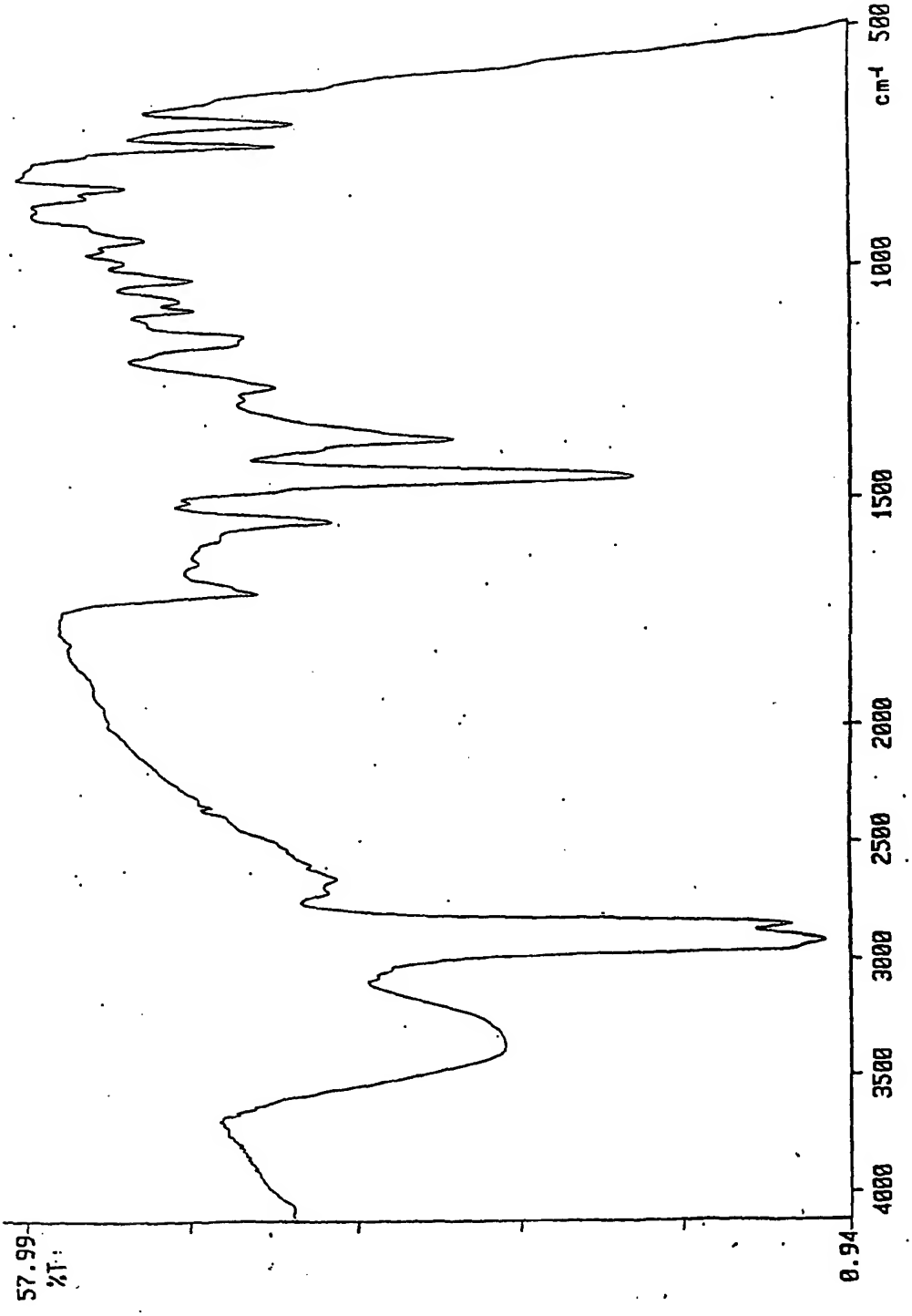
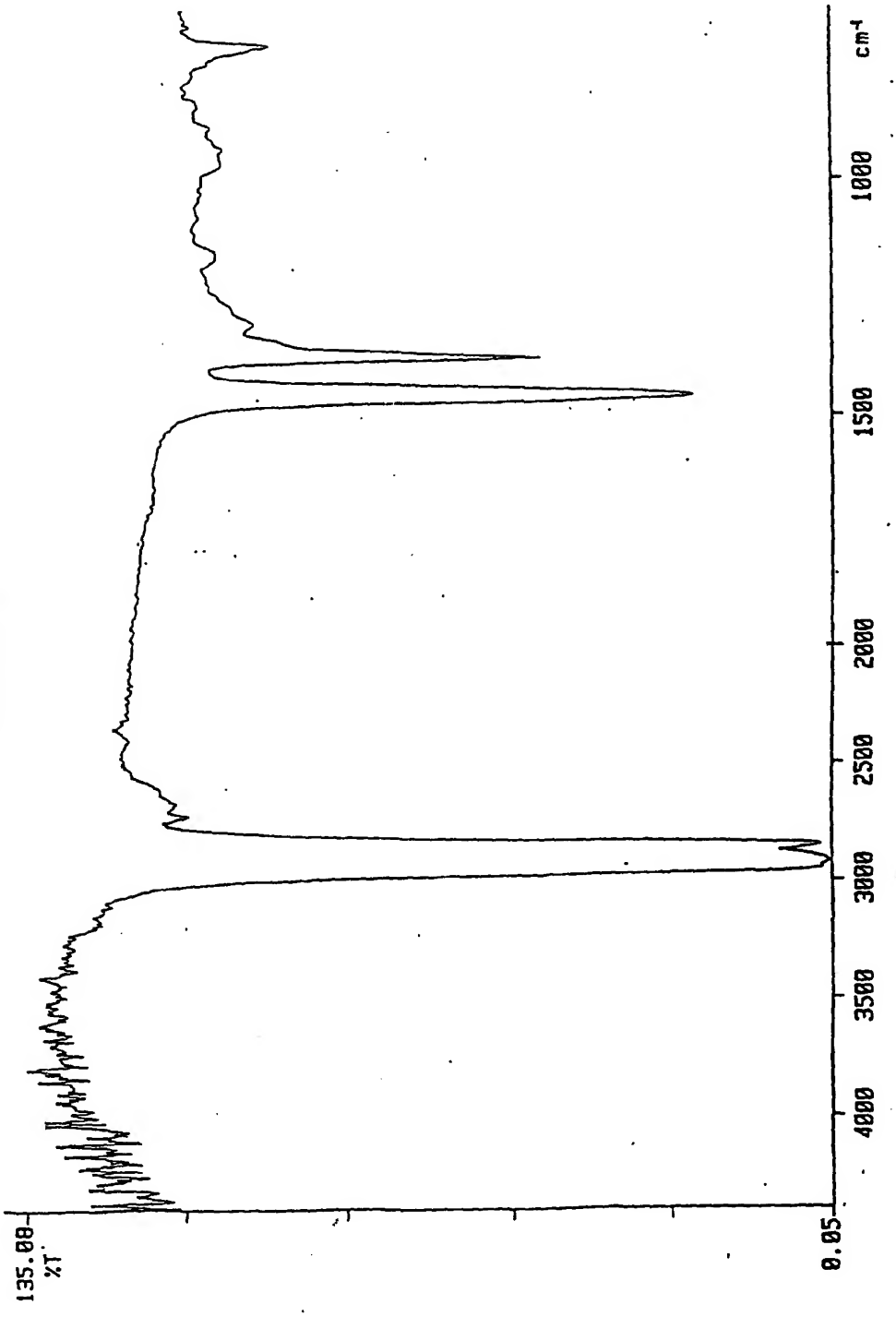


FIGURE 4



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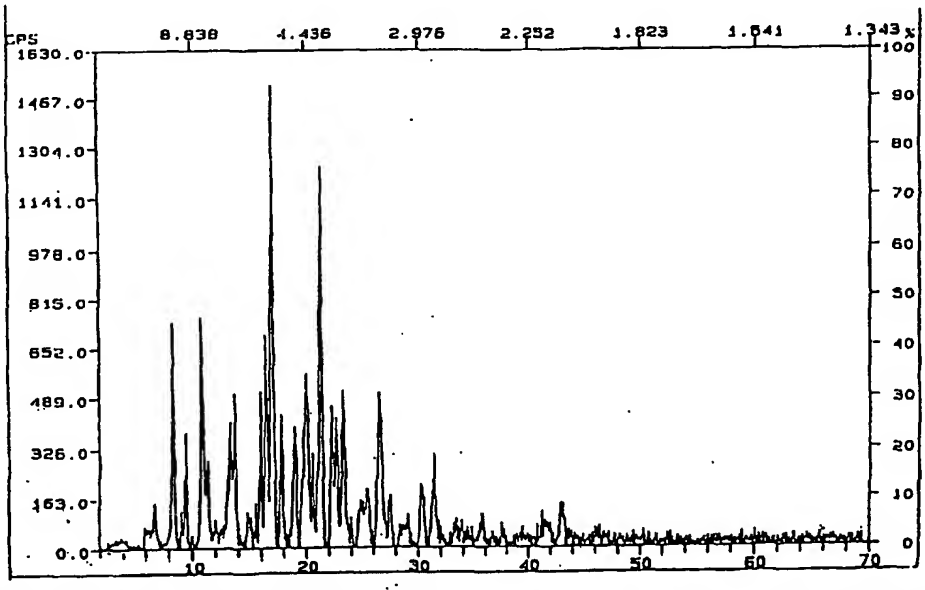
[Continued on next page]

(54) Title: CRYSTAL MODIFICATION OF FEXOFENADINE



(57) Abstract: A novel crystal form of, α-dimethyl-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl]benzeneacetic acid hydrochloride, processes for its preparation and its pharmaceutical use are disclosed.

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Published:
— *with international search report*

(88) Date of publication of the international search report:
4 April 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/18306

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/22 C07D211/34 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 31437 A (MARION MERRELL DOW INC) 23 November 1995 (1995-11-23) cited in the application page 10, line 14 - line 26; claims 3-16 examples	1-23
X	US 5 574 045 A (ORTYL THOMAS T ET AL) 12 November 1996 (1996-11-12) column 3, line 25 - line 47 column 4, line 23 - line 28	1-23
X	WO 95 00480 A (MERRELL DOW PHARMA) 5 January 1995 (1995-01-05) example 45	1-23

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 December 2001	17/12/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Härtinger, S

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/18306

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 00 21510 A (WATTS PETER JAMES ;ILLUM LISBETH (GB); CHENG YU HUI (GB); WEST PHA) 20 April 2000 (2000-04-20) page 9, line 22 - line 27 page 1, line 26 - line 27 ---	1-23
A	WO 99 47693 A (AZERAD ROBERT ;BITON JACQUES (FR); HOECHST MARION ROUSSEL INC (FR)) 23 September 1999 (1999-09-23) page 4, column 27 -column 30; example 1 ---	1-15
P,X	WO 00 71124 A (KHANDURI CHANDRAS HAS ;SHARMA MUKESH (IN); KUMAR NARESH (IN); RANB) 30 November 2000 (2000-11-30) page 1, line 10 -page 3, line 18 -----	1-15

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1(part)-15(part)

Present claims 1-15 relate to particular crystal forms of fexofenadine hydrochloride which have been defined by reference to one or more of the following parameter(s): melting point ranges, x-ray diffraction peaks, NMR signals, IR signals, degree of purity or the process of obtaining the same. The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the fexofenadine hydrochloride as such.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No
PCT/US 01/18306

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Information on patent family members

International Application No
PCT/US 01/18306

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